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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,999	10/28/2003	Ilia Davydov	GRT/4504-2	4116

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EXAMINER	
DESAI, ANAND U	
ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,999	DAVYDOV ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8,10,15,17,35-47 and 57-66* is/are pending in the application.

4a) Of the above claim(s) *5-8,10,15,35-47 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,17,57-63,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to the amendment filed on November 20, 2006. Claims 12, 16, and 55 have been cancelled. New claims 64-66 have been added. Claims 5-8, 10, 15, and 35-47 have been previously withdrawn.

2. Newly submitted claim 64 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the invention is directed to a method of producing a conjugate that depends from withdrawn claim 6. Acknowledgement is made of applicants request for rejoinder. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 64 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Claims 3, 4, 17, 57-63, 65, and 66 are currently pending and are under examination.

Withdrawal of Rejections

4. The rejection of claims 3, 4, 17, and 57-63 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn based on the amendment to claim a conjugate.

5. The rejection of claims 3, 4, 17, and 57-63 under 35 U.S.C. 112, first paragraph, scope of enablement is withdrawn based on the amendment to the claims.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 3, 4, 17, 57-63, 65, and 66 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are directed to an isolated conjugate comprising at least one ubiquitin or ubiquitin derivatized with another molecule, which is employed for purification or visualization, and a protein, wherein said protein is selected from the group consisting of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, HSPC144, Cullin 3, CDC6, and fragments and derivatives thereof, wherein said fragments and derivatives thereof comprise polypeptides of at least 50 amino acids having at least 90% sequence identity to sequences within their corresponding proteins, and said conjugate is formed via N-end rule ubiquitylation of a polypeptide comprising a destabilizing N-terminal residue and an internal Lys residue. The claims are also directed to a conjugate, wherein the protein comprises a recombinant protein, wherein the recombinant protein is selected from the group consisting of tau, and fragments and derivatives thereof (as described above). The claims are directed to a composition comprising a conjugate. The claims are directed to a conjugate made by a process comprising forming a mixture comprising a vector containing a clone coding for said protein, an in vitro transcription/translation system, an N-end

rule ubiquitylation system, and optionally a proteasome inhibitor, and incubating said mixture to produce said conjugate. The conjugate can be immobilized on a support and/or linked to a label.

The specification describes the function for the specific proteins recited in the claims (see page 6, line 10 through page 22, line 23) for example, Aprataxin is a hydrolase that is mutated in ataxia-oculomotor apraxia syndrome. Synaptotagmin-like protein is believed to play a role in regulation of vesicular trafficking. HMG17 is suggested to regulate chromatin structure and gene expression. PinX1 is a RNA processing protein, which inhibits telomerase activity. However, the specification does not describe a specific and substantial utility for the conjugate of ubiquitin or ubiquitin derivative with the respective proteins or the composition comprising the conjugate.

The specification states on page 23, line 1, that applicants have discovered that these proteins are targets for degradation via the N-end rule ubiquitylation pathway, and that controlling the rate of this degradation pathway provides an important mechanism for modulating the levels of these proteins and, thus, controlling disease states that are affected by the levels of these proteins. It is evident that regulating the interaction of the recited protein with ubiquitin would have an effect on the level of the protein, but it is unclear how once the protein already conjugated with ubiquitin can be used to inhibit the ubiquitylation process.

The specification describes methods unrelated to the invention of the conjugate, for example identifying peptides having exposed N-degrons, identifying a protease cleavage site which exposes an N-degron in a protein, identifying proteases which cleave a protein to expose an N-degron, identifying E3 ligases comprising combining a putative E3 with an N-end rule substrate, identifying compounds that modulate N-end rule dependent ubiquitylation, methods of

making pharmaceutical formulation containing one or more active compounds which modulate an N-end rule ubiquitylation, methods for modulating the level of a protein by administering one or more active compounds that modulate the N-end rule ubiquitylation, and a method of changing the susceptibility of a protein to N-end rule ubiquitylation by modifying the protein, possibly by modifying the protein so it no longer comprises the cleavage site (see page 23, line 1 through page 34, line 26). However the claims are directed to a conjugate of the protein already bound to the ubiquitin by the N-end rule ubiquitylation pathway. It is unclear how the protein-ubiquitin conjugate is related to the methods described. It is clear how the protein (not conjugated) could be used to assay for ubiquitin conjugation, which proceeds through the N-end rule pathway, but it is unclear how the conjugate already formed has utility in that assay.

The specification describes the use of N-end rule inhibitors to identify the recited proteins as N-end rule ubiquitin substrates (see Figures 2-11). However, the claims are directed to a conjugate already formed by the N-end rule ubiquitylation pathway. Therefore, based on the supporting written description the claims are not supported by either a specific and substantial asserted utility or a well-established utility.

Claim Rejections - 35 USC § 112, first paragraph

8. Claims 3, 4, 17, 57-63, 65, and 66 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 3, 17, and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. The claims describe the conjugation of a polypeptide comprising a destabilizing N-terminal residue and an internal Lys residue. The conjugate refers to a "protein" as part of the molecule that is conjugated to ubiquitin. The polypeptide should be referred to as protein. What is the polypeptide?

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on (517) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

January 29, 2007

ROBERT A. WAX
PRIMARY EXAMINER